Evidence for defective retinoid transport and function in late onset Alzheimer's disease

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The hypothesis of this article is that late onset Alzheimer's disease (AD) is influenced by the availability in brain of retinoic acid (RA), the final product of the vitamin A (retinoid) metabolic cascade. Genetic, metabolic, and environmental/dietary evidence is cited supporting this hypothesis. Significant genetic linkages to AD are demonstrated for markers close to four of the six RA receptors, RA receptor G at 12q13, retinoid X receptor B at 6p21.3, retinoid X receptor G at 1q21, and RA receptor A at 17q21. Three of the four retinol-binding proteins at 3q23 and 10q23 and the RA-degrading cytochrome P450 enzymes at 10q23 and 2p13 map to AD linkages. Synthesis of the evidence supports retinoid hypofunction and impaired transport as contributing factors. These findings suggest testable experiments to determine whether increasing the availability of retinoid in brain, possibly through pharmacologic targeting of the RA receptors and the cytochrome P450 RA-inactivating enzymes, can prevent or decrease amyloid plaque formation.

Alzheimer's disease (AD), the most common cause of dementia in later life, is a worldwide problem for affected individuals, for their families, and for society at large. Although it involves both genetic risk factors (1) and environmental influences (2), the underlying molecular mechanisms are incompletely understood (3). Effective treatments for preventing the disease, slowing its progression, or alleviating its symptoms are sorely needed.

We propose that vitamin A (retinoid) available from the diet and carried through the body by means of a complex genetic cascade (4) is related to AD. In mice, retinoid modulates early development of brain structure and function (5), and these processes continue into adulthood affecting differentiation, apoptosis, and neuronal signaling (6). Dietary retinoid status has marked effects on adult neuronal functioning, on memory, and on neuronal plasticity (7–9). Up-regulation of retinoid receptor expression alleviates performance deficits in aged mice, supporting the role of retinoids in the cognitive decline associated with aging (10).

Genomic Evidence for a Role of Retinoid in AD

Of the several chromosomal loci identified by genome scans, chromosomes 10q23 and 12q13 are the most frequently associated with AD (11–13). However, no genes have been unequivocally identified by genome screens at any of the AD loci. Remarkably, at each of these loci are found important gene(s) related to retinoids (Table 1). The functions of these genes are discussed below.

Chromosome 12q13. Chromosome 12q13 presents strong evidence for AD linkage (14, 15). Low-density lipoprotein receptor-related protein 1 is a proposed candidate gene, but its role has not been clearly established (14), suggesting that another gene in the vicinity, as yet unspecified and unknown, is causal (16, 17). The retinoid nuclear transcription factor, retinoic acid (RA) receptor (RAR)G lies within 750 kb of AD-linked markers D12S96 and D12S390 (18, 19). Also in the 12q13 band are clustered five of the seven retinol dehydrogenases, which reversibly convert retinol to retinal.

Chromosome 10q23. Chromosome 10q23 harbors the marker D10S583 within the insulin degrading enzyme (IDE) gene (20). This marker is significantly linked to AD, and IDE is a potential candidate as it degrades β amyloid (AB) (21). Although extreme linkage disequilibrium is evident at the IDE locus, at least two groups have found no evidence for linkage of IDE itself to AD, and no polymorphisms in IDE have been associated with AD (22, 23), suggesting that transcriptional regulation rather than translation of the IDE protein may increase vulnerability to AD. Cytochrome P450 26A1(CYP26A1), is 417 kb from IDE. CYP26A1 causes the hydroxylation and degradation of all-*trans* RA (24), and thus controls the availability of RA.

Chromosome 2p13. Chromosome 2p13 has recently been linked to AD plus psychosis (25). A second RA-inactivating enzyme, CYP26A2, is at chromosome 2p13. This CYP is most strongly expressed in the adult cerebellum and pons, and also elsewhere in brain (26). Importantly, this most recent report now establishes genetic links to both CYP26 RA-degrading enzyme chromosomal loci. We suggest CYP26A1 and CYP26A2 as candidates in AD.

Chromosome 17q21. Chromosome 17q21 is the locus of RARA immediately upstream of the anonymous marker D17S1787, which has been recently linked to microtubule-associated protein tau (MAPT)-negative frontal lobe dementia in a single family with a multiple logarithm of odds (MLOD) score of 5.51. This LOD score is among the highest obtained for any dementia linkage. AD could not be excluded in 4 of the 12 cases within this family. Extensive mutation analysis at 17q21 of MAPT including the 5′ region, and Saitohin, another AD candidate gene within MAPT, excluded these two genes, leading the authors to suggest that an unknown gene in the region is responsible (27).

Chromosome 1q21-22. Chromosome 1q21–22 is linked to AD in two genome scanning studies (28, 29). Cellular RA-binding protein 2 (CRABP2) and retinoic X receptor (RXR) G are within the linked region. Both are highly expressed in brain (8, 30). In an AD search, no mutations or polymorphisms were detected in an interval including CRABP2 (31), but RXRG lies just outside of the 14-centiMorgan region sequenced in this study.

Chromosome 6p21.3. Chromosome 6p21.3 is associated with AD in at least three studies (19, 32, 33). Within this band and close to the linked markers is the RXRB.

Chromosome 3q23. Chromosome 3q23 is strongly linked to AD in one study (34). Retinol binding protein (RBP) 1 and RBP2 map to the region.

NEUROSCIENCE

Abbreviations: AD, Alzheimer's disease; AB, amyloid beta; APP, amyloid precursor protein; APOE, apolipoprotein E; CYP, cytochrome P450; EOAD, familial early onset AD; IDE, insulin degrading enzyme; RA, retinoic acid; RAR, retinoic acid receptor; RXR, retinoid X receptor; RBP, retinol-binding protein; TGF-B, transforming growth factor-beta; TTR, transthyretin; MAPT, microtubule-associated protein tau; PS, presenilin.

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Table 1. Chromosomal positions of retinoid cascase genes and AD linkages or associations

Retinoid locus		Alzheimer's disease locus				
Band/Gene	kb	Band/Gene or Marker	kb	cM	LOD/significance	Ref.
12q13		12q13				
RARG	53,518–53,528	D125345–D12578	32,352–104,143	55.25–111.87	LOD 6.374	109
RDH5	56,187–56,192	D12596	53,147	67.16	$P < 0.001$	18
RODH	57,370–57,405	D125390	52,901	67.17	LOD 2.3	19
		D1251632	56,979	71.7	LOD 2.43 APOE4–	110
		LRP1	57,747–57,764	–	O.R. 1.8; $P < 0.01$	24
					No association	23
10q23		10q23				
CYP26A1	94,067–94,071	*IDE*	93,434–93,555	–	$P = 0.04$	20
					Disequilibrium/No linkage	22
RBP4	94,585–94,595	D105583	93,590	115.27	Z max 2.8	20
CYP2C9	95,932–95,982				$P = 0.008$	111
CYP2C8	96,030–96,062	D1051239	102,430	121.81	LOD 2.62	112
2p12		2p13				
CYP26A2/P450RAI-2	72,567–72,586	D251356	43,542	64.29	MLS 3.52	25
17q12-q21		17q12-q21				
RARA	40,640–40,688	D1751787	41,835	70.08	MLOD 5.51	27
1q21.3-q23		1q21.3-q23				
CRABP2	152,434–152,441	D151595–D152844	151,436–160,583	148.85–160.43	No mutations or SNPs	31
RXRG	161,021–161,065			170	MLS 2.67	28
		D15518	182,978	188.02	$P < 0.03$	29
6p21.3		6p21.3				
RXRB	33,158–33,165	*TNFA*	31,597–31,600	51.31	NPL 2.3	32
					$P < 0.03$ APOE+	33
		D651019	38,975	–	LOD 1.3	19
3q23		3q23				
RBP2	140,000–140,028	D353554–D351569	140,435–144,219	146.07–150.58	MLOD 4.17 plaque only	34
RBP1	140,065–140,088					
9q34.3		9q34.2				
RXRA	129,062–129,102				MLS 1.96	113

Chromosomal positions as band, kilobase (kb), centiMorgan (cM) for selected genes of the retinoid cascade and genes or markers linked to AD at those loci. Markers and genes were located using the Locus Link database (http://www.ncbi.nlm.nih.gov/LocusLink/) posted as of January 22, 2003. Where available, the DeCode position was reported.

We examined the loci connected to familial early onset AD (EOAD), and found that, with the exception of one or two rare mutations in single pedigrees, none of them is near loci of genes of the retinoid cascade nor the retinoid nuclear receptors. On the other hand, as Table 1 shows, there is a consistent relationship between areas in the genome repeatedly linked to AD and the loci of genes in the retinoid metabolic cascade, retinoid transporters, the retinol binding proteins and the retinoid nuclear receptors. We propose these retinoid genes at AD-linked loci as specific candidates for AD.

Functions of Retinoid-Related Genes

The above finding of colocalization of AD loci and retinoid-related genes suggests that retinoids have a role in the disease.

How could mutations of these retinoid-related genes be involved in AD, as suggested by their colocalizations with AD loci? Experiments have been performed that support a major role of retinoids in AD. Expression of AD-related genes depend on RA in the brain, as presented in the following review of the literature. The retinoid metabolic cascade determines the amount of RA. Three steps involved are retinoid in the diet, its transport to the brain, and availability of RA, the functional end product of the cascade. Mutations that affect the retinoid cascade could alter the level of RA in the brain. And mutations in genes coding for the RARs and RXRs could modify transcriptional functioning of genes activated by the RA/retinoid receptor complexes. In this section, a description of functions of the genes of the retinoid cascade is provided with special reference to those at AD loci.

Genes Involved in Retinoid Transport. Vitamin A is essential for life. It cannot be synthesized by humans, and therefore must be supplied in the diet as ingested beta-carotene from plant products or as chemically synthesized retinol (35, 36). Retinoid transport from the intestine is necessary for its storage in target tissues including brain (37), and this transport appears to be modified in AD. The distribution of RA within the mature human central nervous system is unknown (38), but there is indirect evidence supporting lowered concentration of RA in the Alzheimer brain. This is because it is, of course, impossible to sample live human brains, and RA is rapidly degraded by CYP26 (24) in autopsy brains. However, elevated levels of retinaldehyde dehydrogenase (RALDH), the enzymatic synthesizer of RA, are found in Alzheimer brains, and these levels are consistent with a feedback mechanism in which neuronal cell lines starved of retinoid demonstrated increased RALDH, which is normalized by addition of retinol (38). In addition, there are multiple reports of lowered levels of antioxidants, including retinoid, in serum or plasma of AD patients compared with controls (39–41), which, we argue, is consistent with altered levels in the Alzheimer brain. These lowered levels appear to be specific to AD, because no such differences are found in a general population of aged humans with memory impairment (42). Vitamin-A-depleted mice have profound impairment of hippocampal long-term potentiation and depression resulting in memory defects, which

are rescued by the addition of RA directly to the mouse brain (9). This rescue is accompanied by up-regulation of the expression of RARs in the brain (10).

Retinyl esters are transported from intestine to stellate cells in liver for storage and to target tissues by a highly regulated process dependent on the assembly and secretion of chylomicrons (43). Apolipoprotein E (APOE) is a transport protein for retinyl esters in chylomicrons (37). This is one of the alternative and redundant pathways by which necessary retinoid is made available to various target tissues. Several properties place the retinyl ester/APOE complex in a pivotal position for impacting the transcription of retinoid-regulated target genes. The APOE2 allele clears postprandial chylomicron remnants containing retinyl esters more slowly than do APOE3 or APOE4 (44). APOE4 is strongly associated with increased risk for AD of both early and late onset by genetic and clinical studies (for review see refs. 45 and 46). APOE2 apparently is protective against AD (47, 48). APOE regulates the transport and synthesis in neuronal membranes of docosahexaenoic acid (49), a ligand for the RXRs (50). Docosahexaenoic acid has recently been shown to protect against memory impairment in rats (51). In feedback fashion, the transcriptional expression of APOE in brain astrocytes is strongly up-regulated by RA (52).

At high retinyl ester concentrations, diffusion of retinol into cells in the nervous system is enabled by transporters other than APOE (53), e.g., the lipocalin apolipoprotein D (54). Apolipoprotein D expression is regulated by RARA (55), and increased in stressed neurons of AD patients (56), as well as in normal aging, before the accumulation of neurofibrillary tangles (57). We suggest that the increased expression may be the result of feedback mechanisms dependent on the reduced amounts of retinol in aging individuals (58). This lipoprotein transport system markedly affects amyloid precursor protein (APP) processing and AB plaque formation (46).

RBPs are the major carriers of retinol and titrate the availability of retinol throughout the body (36, 59). They are able to carry retinol alone as well as in complex with transthyretin (TTR). TTR is the major carrier of retinol bound to RBP from liver stores through plasma to target tissues. Both RBP alone and complexed with TTR can transport retinoid across the choroid plexus (4, 60). RBP and TTR are produced in the fourth ventricle of the brain and are abundant in cerebrospinal fluid (61). TTR expression in hippocampus was recently reported (62), and TTR interacting with insulin growth factor 1 may actively degrade and remove AB from the hippocampus (63).

Genes Involved in Retinoid Metabolism. RA, the final and morphogenic product of the retinoid cascade, is synthesized from retinal (35). Lipoprotein lipase releases retinol from its ester and is highly expressed in the hippocampus (64). Retinol is oxidized in two steps, reversibly to retinal by retinol dehydrogenases and then irreveribly by retinaldehyde dehydrogenases to produce the several forms of RA (5). RA is highly efficiently synthesized in the adult hippocampus in rats (59). Degradation of RA, which also controls the level of RA, is initiated by hydroxylation catalyzed by enzymes CYP26A1 and CYP26A2 in the brain (24, 65).

RAR Functions. The main function of RA is to modulate gene transcriptions by liganding nuclear receptors that bind to their DNA response element motifs in promoters of target genes (66). The three RXRs are involved in all retinoid signaling cascades (67), and all are expressed in the adult brain (68). Some of the many genes activated are involved in cognition and the sustainability of long term potentiation and depression necessary in learning, memory, brain formation and neurotransmitter functioning (6–10, 68, 69).

A specific decline (20–30%) was reported in levels of mRNAs of the retinoid receptors RARB and RXRB/G in the hippocampus of aged mice (10). We propose that mutations of the retinoid receptors RARG at 12q13, RXRG at 1q21, RARA at 17q21 and RXRB at 6p21.3, can misregulate AD candidate genes, according to the availability of RA, because these receptors' genes have been repeatedly linked to AD loci (Table 1). For example, the RARG/RXRG heterodimer activated by RA up-regulates the expression of the RA-degrading enzyme CYP26A1, (70). RA thereby influences its own removal.

Functions in AD of Retinoid-Related Genes

We hypothesize that allelic variants that increase vulnerability to AD will be found to modulate transcription of genes known to be mutated in EOAD. Mutations in three genes, AB, amyloid precursor protein (APP), presenilin (PS)1, and PS2, have been identified as having direct effects in EOAD (1). Although numerous other genes, e.g., beta-site APP-cleaving enzyme (71), are required in the molecular processing to produce amyloid plaques and/or neurofibrillary tangles, with rare exceptions, no other genes have yet been generally found to be directly mutated in classical EOAD or AD. However, the APOE4 variant increases susceptibility to both early and late AD (45, 46, 72).

Many of the genes involved in these processes are retinoid target genes. RA receptors plus ligand regulate the expression of genes in a variety of cell types in the brain including, among others, MAPT (73, 74), APP (74–78), PS2 (79), and beta-site APP-cleaving enzyme (80). IDE degrades amyloid plaque and is present in brain (21, 81). IDE transcription is regulated by RA; the gene contains a RARA response element in its promoter (82). APP as precursor contributes to AB synthesis, but is not itself neurotoxic and promotes neurite outgrowth (75, 78). RA has been shown to regulate the MAPT promoter (73). We have inspected the nucleic acid sequence of MAPT (83) and determined that it contains a RAR response element, TGAACxxTGAAC (84), beginning at 5′ −16. There are four different TGACC motifs throughout the gene, which also may confer retinoid responsivity (85, 86). We suggest that the transcriptional activation of these elements may be modified by variants of one or another of the RARs.

Transcription of APP, in addition to regulation by RA (74–78) is also positively regulated by transforming growth factor beta (TGF-B), a cytokine centrally involved in AD, plaque formation (87), brain injury, and inflammatory responses (88). Terminally differentiated neurons expressing TGF-B2 receptors appear to be protected from AB toxicity by the administration of TGF-B2 (89), which reduces plaque burden in transgenic mice (90). TGF-B2 pathways are up-regulated by RA and diminished under conditions of retinoid deficiency (91). TGF-B2 is strongly restored by RA in tissue-specific fashion in retinoid deficient rats (92). Thus, RA may increase production of APP in normal neurons in part via the TGF-B pathway involving SMAD4, which is stained strongly in AD brain (87).

Reports indicate that TTR may clear or prevent formation of AB, and higher levels of TTR appear to diminish amyloidogenicity (63, 93, 94, 95). Lower levels of TTR have been reported in AD (96), but no mutations in TTR are identified in an Alzheimer sample (97). Increased TTR has other effects, namely to stabilize RARG2, and also to decrease response of this receptor to RA. This is accomplished through inhibition of the kinase cascade (98).

All of the above existing experimental results support our hypothesis that hypofunctioning of retinoid is a key factor in development of AB toxicity. This is particularly relevant in light of the age-related decline in retinoid supply in both normal and AD samples (38–41, 58). To determine whether genetic variations in the retinoid genes at loci linked to AD increase vulnerability it will be necessary to sequence these specific candidates in coding, 5′, 3′, and promoter regions.

Epidemiologic Findings Relating Retinoid to AD

Retinoid supplementation is prominent in the rescue of function of retinoid-deficient cells and tissues (7–10, 92). A remarkable epidemiological finding that provides a clue for etiology and risk factors for AD has recently been reported. The age-standardized rate of AD is more than double among African Americans in Indianapolis than among a comparison sample of Africans in Ibadan Nigeria (2, 99). No explanation has been offered. The researchers reported that the diet among the Ibadan community consists mainly of red palm oil and yams (Hendrie as quoted in The New York Times, February 14, 2001). This diet, high in provitamin A (100, 101), should maximize the levels of retinoid available for adequate storage in target tissues (37) and transport to brain by APOE (53) and other retinoid transporters, e.g., apolipoprotein D (54) and TTR (60). Consistent with this hypothesis, APOE4 is not a risk factor for AD in Ibadan (99). The findings from this initial crossnational epidemiologic study are well worth replication with other samples.

Applications to Prevention, Therapy, and Detection

If additional experimental evidence supports our hypothesis, modulation of the disease by changing the level of RA in the brain through dietary or pharmacological intervention is suggested. RA has been used systemically in therapies against acne and cancers; it is, however, toxic at high concentrations. Thousands of RA analogs have therefore been synthesized in efforts to diminish toxicity relative to efficacy and ligand specificity. Some of these might be effective against AD (10, 102). A less toxic alternative might be with retinyl esters, bound to chylomicrons (37).

A variety of potential therapies come to mind for future testing. Drugs could induce enzymes that increase RA synthesis, in particular, in the hippocampus (103) and other areas involved in AD pathology. In contrast, homocysteine, the level of which is increased in AD, has the opposite effect of inhibiting RA synthesis (104, 105). Inhibition of the CYP26 RA-degrading enzymes at the 10q23 and 2p13 loci linked to AD is an approach not previously suggested. Specific CYP26 inhibitors, e.g., liarazole (106), could be applied to increase RA; low concentrations may be necessary because xenobiotics frequently induce proteins involved in their detoxification (107). The increased specific ligation to the RARG/RARA heterodimer regulating IDE transcription (90) might cause plaque degradation by increasing IDE (20, 21). Ligands that increase TTR should increase retinoid in the brain, and the down-regulation by increased TTR of p38 mitogen-activated protein kinase (63) might spare RARG2 from phosphorylation and degradation (98). Alternately, the RARG/RXRG heterodimer regulating the atypical expression of CYP26A1 (70) could be manipulated by receptor ligand antagonists. The above suggestions involve targeting RARG.

Without further basic and pharmacological knowledge, the complexity of retinoid regulations in the central nervous system and the remarkably wide range of regulatory and signaling processes in which retinoids are involved could make successful implementation of these strategies difficult to accomplish safely. Although pharmacologic strategies to increase retinoid activation in brain may in this early stage seem far-fetched, recall the remarkable success against heart disease when dietary and drug measures were developed and applied to lower cholesterol after this molecule was identified as a major risk factor (108).

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